NTP
National Toxicology Program

Divinylbenzene-HP

Toxicology and Carcinogenesis Studies of Divinylbenzene-HP in F344/N Rats and B6C3F1 Mice

(Inhalation Studies)

NTP
National Toxicology Program

Copolymer and Cross-linking Agent

- Styrene
- Butadiene
- Methacrylic acid
- Acrylic acid
- Vinylbenzyl chloride

- Increase stress resistance
- Chemical resistance
- Heat distortion
- Hardness
- Impact strength

NTP
National Toxicology Program

Products

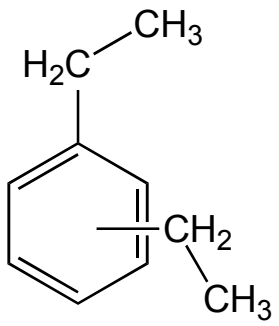
- Adhesives
- Plastics
- Elastomers
- Biological materials
- Coatings
- Catalysts
- Membranes
- Pharmaceuticals
- Ion exchange resins

NTP
National Toxicology Program

Nominated By NCI

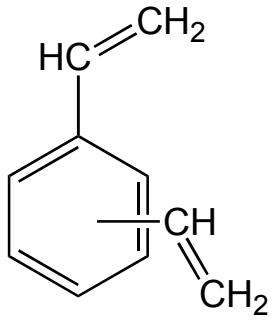
- Toxicology and carcinogenesis
- Inhalation route
- Potential for human exposure
- Lack of toxicity and carcinogenicity data
- Structural similarity to benzene and styrene

Divinylbenzene High Purity (HP)



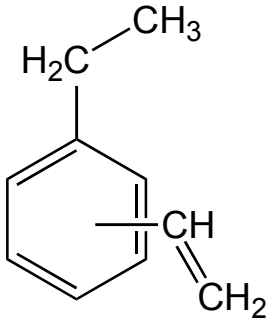
m,p-Diethylbenzene

80%



m,p-Divinylbenzene (DVB)

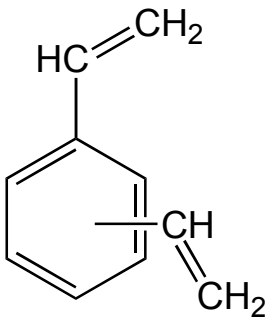
20%



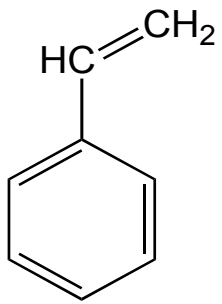
m,p-Ethylvinylbenzene (EVB)

NTP
National Toxicology Program

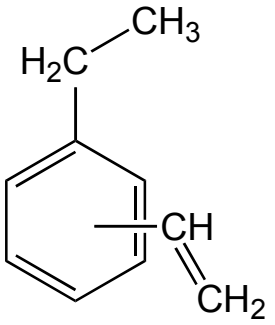
Oxidative Metabolism of DVB-HP



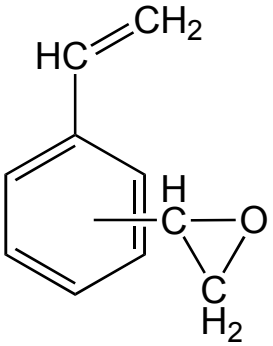
DVB

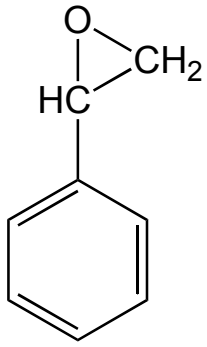


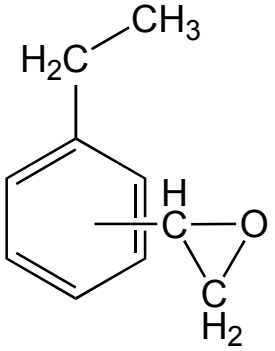
Styrene



EVB







NTP
National Toxicology Program

2-Week Study Design - Rats

- Male and female Fischer 344 rats
- 5 animals / sex / concentration
- 0, 25, 50, 100, 200, 400 ppm DVB-HP
- 6 hr / day, 5 days / week, 16 days

NTP
National Toxicology Program

2-Week Study Results - Rats

- Survival – 100%
- Body weights – 8 -10% decrease at 400 ppm
- Potential target sites:
  - Lung, liver, kidney – ↑ organ weights
  - Nose - minimal to mild rhinitis (400 ppm)

- Selected same concentrations for 3-month study

NTP
National Toxicology Program

3-Month Study Design - Rats

- 0, 25, 50, 100, 200, 400 ppm DVB-HP
- 6 hr / day, 5 days / week, 14 weeks
- Core - 10 rats / sex / concentration
- Clinical Pathology – days 3, 23, 90
- Sperm motility, vaginal cytology (SMVCE)

NTP
National Toxicology Program

3-Month Study Results - Rats

- Survival – 100%
- Body weights - no effect
- Organ weights – minimal increase (liver, kidney)
- Clinical Pathology – minimal transient effects
- Histopathology – nose, olfactory epithelium
  - minimal to mild degenerative / regenerative changes
- SMVCE – no effect

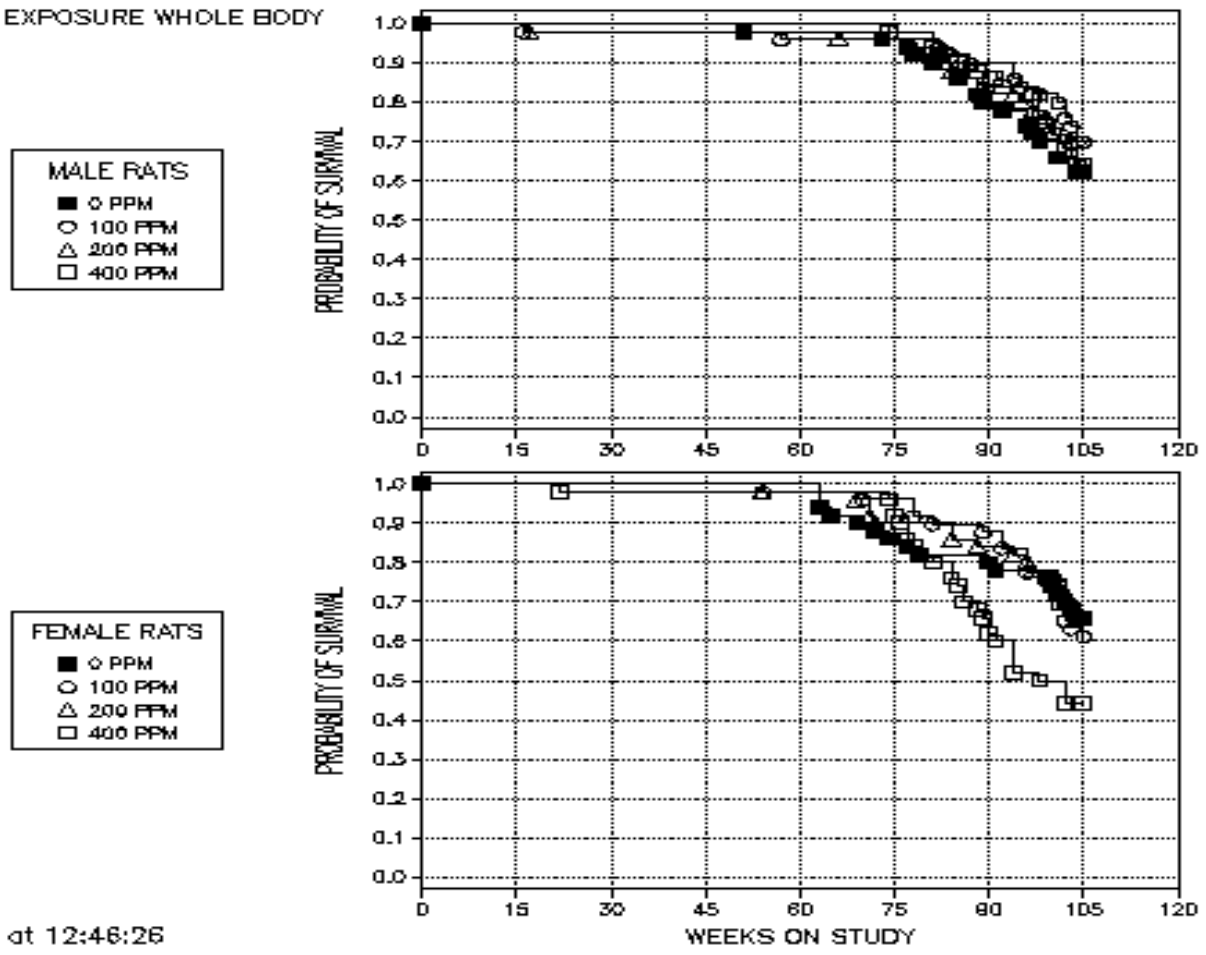
NTP
National Toxicology Program

2-Year Study Design - Rats

- 0, 100, 200, 400 ppm DVB-HP
- 6 hr / day, 5 day / week, 105 weeks
- 50 rats / sex / concentration

Survival - Rats

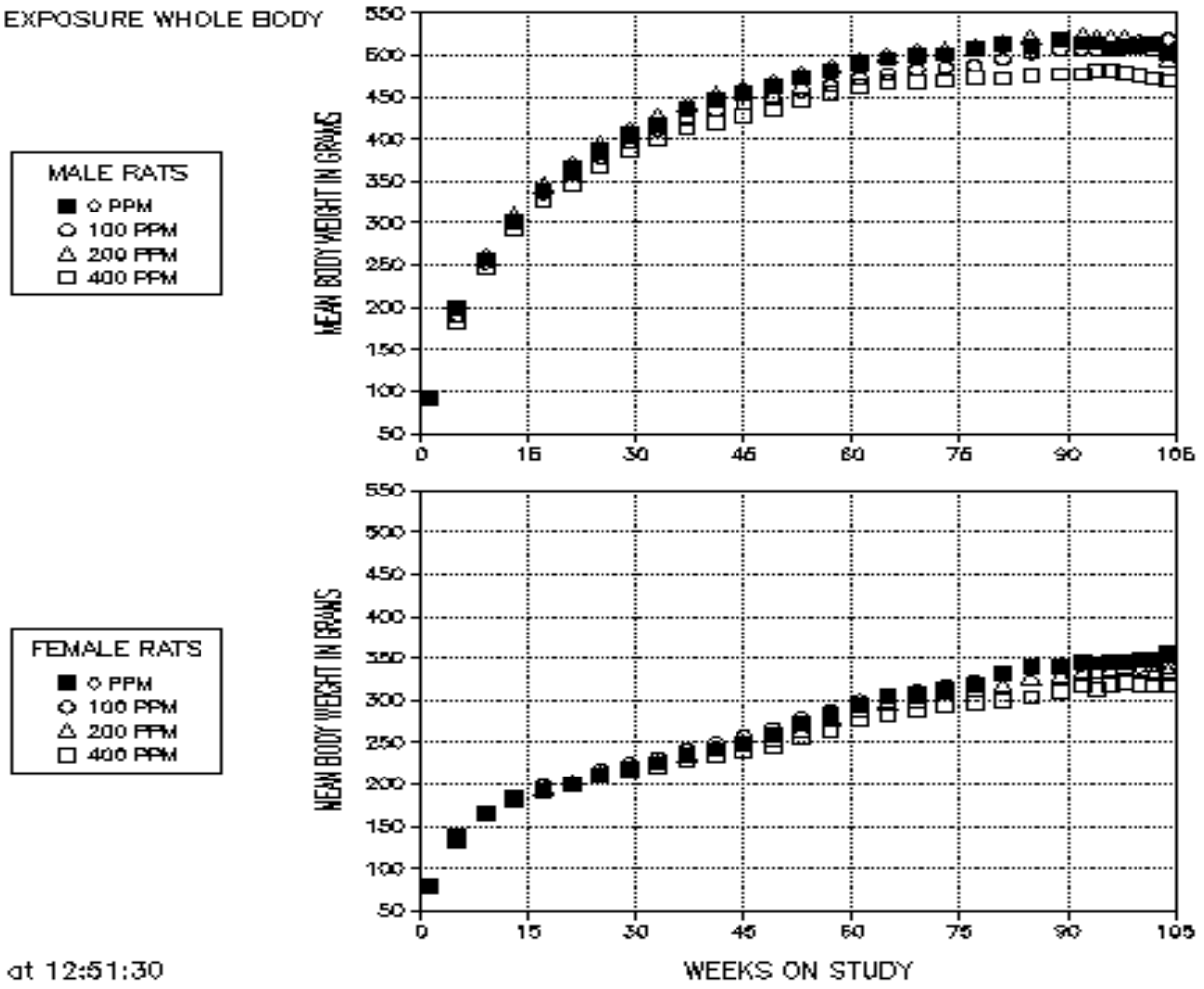
DIVINYLBENZENE
ROUTE: RESPIRATORY EXPOSURE WHOLE BODY
EXPT: 88004
TEST: 05



Produced on 20JAN04 at 12:46:26

Body Weights - Rats

DIVINYLBENZENE
ROUTE: RESPIRATORY EXPOSURE WHOLE BODY
EXPT: 88004
TEST: 05



Produced on 20JAN04 at 12:51:30

NTP
National Toxicology Program

2-Year Study Results - Rats

- Nonneoplastic lesions
  - Nose: olfactory epithelium (most exposed rats)
    - degeneration/regeneration
    - Bowman's glands, dilatation

- Neoplastic lesions
    - kidney, brain

NTP
National Toxicology Program

Male Rat Kidney Neoplasms

Single Sections	0	100	200	400 ppm
Renal tubule hyperplasia	1 (2.0)	2 (1.0)	0	2 (4.0)
Renal tubule carcinoma	0	0	0	2

Incidence of carcinoma (2/50) is not significantly different from incidence in concurrent controls; exceeds historical incidence 1/399.

Single + Step Sections	0	100	200	400 ppm
Renal tubule hyperplasia	3 (1.3)	5 (1.0)	5 (1.4)	16*(2.0)
Renal tubule adenoma	0	0	2	1
Renal tubule carcinoma	0	0	0	2
Combined	0	0	2	3

Marginal increase in renal tubule carcinomas may be treatment related.

NTP
National Toxicology Program

Rat Brain Neoplasms

Male	**0**	**100**	**200**	**400 ppm**
astrocytoma	0	0	2 /50	0
oligodendroglioma	0	1/50	1/50	0
combined	0	1/50	3/50	0
Female				
astrocytoma	0	0	1/50	0

Tumor incidences alone or combined are not significantly different from concurrent controls, but exceed the historical incidence (combined oligodendroglioma or astrocytoma) in chamber controls: 1/398.

Marginal increase in rare, malignant glial cell tumors may be treatment related.

NTP
National Toxicology Program

2-Week Study Design - Mice

- Male and female B6C3F1 mice
- 5 animals / sex / concentration
- 0, 25, 50, 100, 200, 400 ppm DVB-HP
- 6 hr / day, 5 days / week, 17 days

NTP
National Toxicology Program

2-Week Study Results - Mice

- Early deaths:
  - 400 ppm – 100% mortality
    - Liver – hepatocellular degeneration, loss & hemorrhage
  - 200 ppm - 40% mortality
    - Liver – necrosis
    - Nose – necrosis of nasal and glandular epithelium
- Survivors:
  - 200 ppm
    - Liver - hepatocellular karyomegaly and hypertrophy
    - Kidney – tubular necrosis, regeneration, mineralization
  - 25 – 200 ppm
    - Nose – nasal and glandular epithelial metaplasia

NTP
National Toxicology Program

3-Month Study Design - Mice

- 0, 12.5, 25, 50, 100, 200 ppm DVB-HP
- 6 hr / day, 5 days / week, 14 weeks
- Core: 10 mice / sex / concentration
- Histopathology
- SMVCE, hematology at 14 wk

NTP
National Toxicology Program

3-Month Study Results - Mice

- Early deaths (200 ppm)
  - 10/10 male, 9/10 female
  - necrosis of liver, kidney, nose
- Survivors (25, 50, 100 ppm)
  - Body Weights - >10% decrease
  - Nose olfactory epithelium - degeneration
  - SMVCE – no effect
  - Hematology – minimal effects
  - Micronuclei - negative

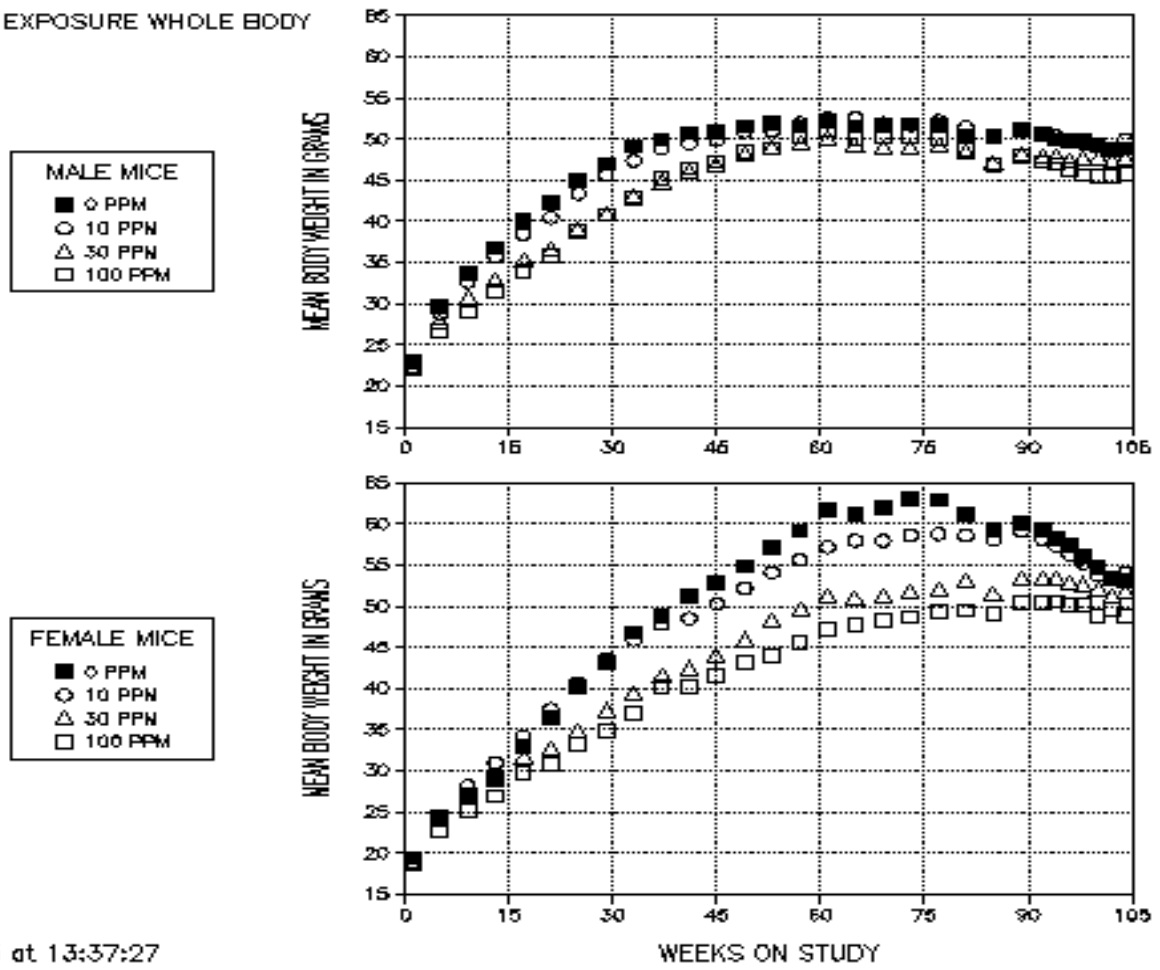
NTP
National Toxicology Program

2-Year Study Design - Mice

- 0, 10, 30, 100 ppm DVB-HP
- 6 hr / day, 5 day / week, 105 weeks
- Core: 50 mice / sex / concentration
- Histopathology

Body Weights - Mice

DIVINYLBENZENE
ROUTE: RESPIRATORY EXPOSURE WHOLE BODY
EXPT: 88004
TEST: 08



Produced on 09SEP03 at 13:37:27

NTP
National Toxicology Program

2-Year Study Results - Mice

- Survival - no effects
- Nonneoplastic lesions
  - Lung – hyperplasia: alveolar epithelial, bronchiolar, atypical
  - Nose – inflammation, metaplasia of olfactory & glandular epithelium
- Neoplastic lesions
  - Lung

NTP
National Toxicology Program

Lung Neoplasms in Male Mice

Male	**0**	**10**	**30**	**100 ppm**
bronchiolar hyperplasia, atypical	0	38*(1.1)	46*(1.8)	46*(2.0)
alveolar epithelium, hyperplasia	1 (1.0)	5 (3.2)	5 (2.0)	7*(2.0)
alveolar/bronchiolar adenoma	12	6	6	15
alveolar/bronchiolar carcinoma	5	4	3	9
adenoma or carcinoma (combined)	16/49 (34.7%)	10/49 (21.9%)	8/49 (17.4%)	20/49 (42%)

Historical incidence of adenoma or carcinoma in chamber controls: 115/349 (33 $\pm$ 6%), range 26 - 44%.

NTP
National Toxicology Program

Lung Neoplasms in Female Mice

Female	**0**	**10**	**30**	**100 ppm**
bronchiolar hyperplasia, atypical	0	39*(1.3)	45*(1.8)	48*(2.1)
alveolar epithelium, hyperplasia	4 (1.8)	3 (1.7)	4 (2.3)	8 (2.5)
alveolar/bronchiolar adenoma	4	9	4	8
alveolar/bronchiolar carcinoma	2	5	4	5
adenoma or carcinoma (combined)	6/50	12/50	8/50	13/49
	14.1%	26.7%	17.9%	27.7%

Historical incidence of adenoma or carcinoma: 27/349 (7.8 $\pm$ 4.3%, range 2- 14%).

NTP
National Toxicology Program

DVB-HP Genetic Toxicology

- Negative in Salmonella strains TA97, TA100, TA1535, TA1537, with and without S9.

- No increase in frequency of micronuclei, or the % polychromatic erythrocytes in peripheral blood.

NTP
National Toxicology Program

Conclusions

- Equivocal evidence in male rat (kidney, brain)
- No evidence in female rat
- No evidence in male mouse
- Equivocal evidence in female mouse (lung)

NTP
National Toxicology Program

NTP Technical Reports Review Subcommittee Meeting

Divinylbenzene-HP

TR 534